COMMENTS TO THE SAB ON THE PANEL RECOMMENDATIONS ON THE EPA DRAFT RISK ASSESSMENT FOR LIBBY AMPHIBOLE ASBESTOS

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We have been following the EPA risk assessment process for Libby amphibole asbestos (LAA) and have made detailed comments to the special SAB panel set up to review the first EPA draft of the risk assessment. We have a number of concerns that were laid out in our previous comments to the panel and to the Agency, and we refer the SAB to those comments. One of us (SM) reviewed the draft in detail when it first appeared in 2011 and provided detailed written and oral comments to the Agency. In the comments below, we would like to raise two fundamental issues with the risk assessment as it stands, one procedural, and the other scientific. The procedural issue relates to the extremely limited manner in which public participation in the risk assessment process has been conducted to date. The scientific issue relates to an analysis of relevant data that EPA failed to provide to the public. The EPA was unwilling to release for analyses the full dataset with all covariates on which its risk assessment for non-cancer endpoints was based. The data were originally collected by the University of Cincinnati (Rohs et al., 2008). Under a FOIA request to the University of Cincinnati, we recently acquired and analyzed the data that forms the basis of the Agency's non-cancer risk assessment. We summarize the results here.

Procedural Issue

1. There was little opportunity for meaningful scientific dialogue with the panel during public meetings. We can understand that when a substantial number of individuals signs up to make comments, it is necessary to enforce a strict time limit on individual comments. However, this was not the situation at these panel meetings. At the discretion of the Chair and the Agency, it should have been possible for members of the public to engage in a meaningful scientific dialogue with the panel. We were denied that opportunity.
2. We understand that it is necessary to have multiple disciplines represented on the panel. However, the most controversial issues usually revolve around the interpretation of the analyses of dose-response data, particularly when these are epidemiologic data. This was clearly the case with this risk assessment for both the cancer and non-cancer endpoints. There were only two panel members who appeared to be comfortable with the more arcane statistical issues, and they were sharply divided in their scientific opinions. Clearly, the panelist who had serious problems with the Agency analyses chose not to submit a minority report. However, the panel report that the full committee is reviewing today purports to present a consensus that was never evident during the public discussions.

Scientific Issue

In a precedent-setting move, the Agency is proposing a reference concentration (RfC) for LAA based on a non-cancer endpoint. The proposed RfC for LAA, which will likely be applied to all forms of asbestos, is 0.00002 fibers/cc, which is below background levels of asbestos in many parts of the country. The Agency uses pleural plaques as the endpoint for derivation of the RfC, contending that pleural plaques are not just markers of asbestos exposure, but are adverse health effects associated with decrements in pulmonary function and other more serious conditions. We believe that this position has little scientific support as we have pointed out to the panel in our previous comments. We do not wish to re-argue this

issue here. We simply point out that the panel recommendations to the Agency on this matter contain serious factual inaccuracies that should be corrected. For example, for pulmonary function, the panel report refers to the American Thoracic Society 2004 report and recommends the addition of 3 additional references (Lilis 1991, Paris 2009, Clin 2011). Paris 2009 does not even discuss pulmonary function and Lilis 1991 is the ATS 2004 reference (112) in the following quote concerning plaques and FVC: "This has not been a consistent finding (110, 111) and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques (112). Decrements, when they occur, are probably related to early subclinical fibrosis." The SAB panel specifically lists references used by the ATS 2004 report some of which are incorrect including some that were clearly published several years after the ATS report.

The derivation of this RfC is based on the prevalence of pleural plaques in a small sub-cohort of the full Rohs cohort. Whereas the full Rohs cohort consists of 280 subjects with 68 cases of pleural plaque, the sub-cohort on which EPA bases its RfC consists of 118 individuals with 12 pleural plaques. The table below shows the distribution of cases of pleural plaque in this sub-cohort by deciles of cumulative exposure. It is clear that there is little information in this sub-cohort for a proper dose-response analysis.

Decile	Exposure (f/cc-yr)	Cases	Subjects	Prevalence
1	0.02	1	12	0.08
2	0.04	0	12	0.00
3	0.07	1	12	0.08
4	0.09	0	12	0.00
5	0.11	0	11	0.00
6	0.14	1	12	0.08
7	0.22	2	12	0.17
8	0.32	2	12	0.17
9	0.50	1	12	0.08
10	2.29	4	11	0.36

Table 1: The sub-cohort used by the EPA for derivation of the RfC by deciles of exposure. The second column labeled "Exposure" is the average cumulative exposure in each decile. It is clear that any dose-response relationship is driven by the cases (number of individuals with plaque) in the highest decile.

We have analyzed both the sub-cohort used by the Agency and the full Rohs cohort. We present a brief summary of our findings here. These indicate clearly that the results in the sub-cohort are highly inconsistent with the results in the full cohort. These results indicate also that these data cannot be used for estimation of an RfC using the simplistic approach the Agency has adopted.

In both the full Rohs cohort and the sub-cohort, it is possible to perform dose-response analyses with three distinct measures of 'dose', cumulative exposure (ce), concentration, and duration of exposure.

1. The sub-cohort is too small to distinguish among models, with many models yielding virtually identical fits as judged by the Akaike Information Criterion (AIC). Nonetheless, the logistic regression model with concentration as the measure of 'dose' describes the data best as judged by the AIC, i.e., has the lowest AIC. Furthermore, concentration is the only measure of 'dose' that is statistically significant in these data. Despite this fact, the Agency has based its RfC on the Michaelis-Menten model with ce as the measure of 'dose'. With only 12 pleural plaques, the dataset is not large enough to test the impact of confounders, such as age and body mass index (BMI). The panel recommended that the EPA use the dichotomous Hill model with ce as the measure of exposure and with two parameters (the background and the plateau) fixed at highly uncertain values derived from epidemiologic studies. We have implemented this model and find that the logistic regression model with concentration as the measure of 'dose' describes the data as well as the constrained dichotomous Hill model. Thus, these data are too small to distinguish between the logistic regression model with concentration as a measure of 'dose' and the constrained dichotomous Hill model with ce as the measure of 'dose'. Clearly, these data should not be used for the estimation of an RfC. As noted below, however, when we analyzed the original Rohs data, which has far more pleural plaques than the sub-cohort (68 versus 12), the constrained dichotomous Hill model is resoundingly rejected.
2. In the full Rohs dataset, duration of exposure is by far the best measure of 'dose'. In fact, it is clear that the probability of pleural plaque is a function of both concentration and duration of exposure and, therefore, ce is a poor measure of 'dose'. Age is a strong confounder, with the coefficients for any of the measures of 'dose' becoming substantially attenuated when age is included in the regression model. Furthermore, the probability of plaque is a non-linear function of duration. The median duration of exposure in this cohort is about 25 years. With the data stratified on duration, there is no evidence of an association of any measure of 'dose' with probability of pleural plaques for durations of exposure less than 25 years. It is clear from these

analyses that there is no straight-forward way to estimate an RfC from these data. In fact, if there is no evidence of an association of exposure with probability of plaques for durations of less than 25 years, then the whole concept of a reference concentration needs to be reconsidered.

3. The constrained dichotomous Hill model recommended by the panel does a very poor job of fitting the full Rohs dataset.
4. Both the Agency and the panel appear to have lost sight of a fundamental fact. Since the point of departure (POD) is the lower 95% confidence limit on the benchmark dose (BMD), the greater the uncertainty in the data, the lower the POD. Therefore, in general, small data sets will lead to lower PODs than large datasets because the confidence interval on the BMD is inversely related to the size of the dataset. This is another important reason not to base RfCs on small datasets, such as the one used by the Agency in this risk assessment.

Recommendation

The full SAB should return this risk assessment for reconsideration by the panel.